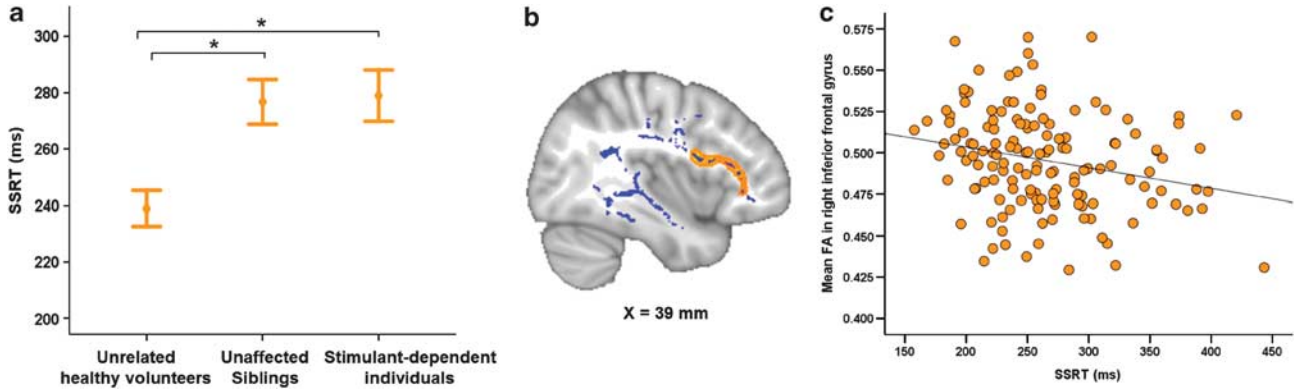

Figure 1. Deficits of motor inhibitory control and white matter organization in stimulant-dependent individuals and their non-dependent siblings. (a) Stop-signal reaction time (SSRT) differed significantly between the three groups ($F_{2,141} = 9.9$, $P < 0.001$). SSRT was significantly prolonged in both the stimulant-dependent individuals and their siblings compared with unrelated healthy volunteers (Bonferroni $P \leqslant 0.005$, for both comparisons). (b) The skeleton of group differences in mean fractional anisotropy (FA) is colored in blue ($F_{2,141} = 26.3$, $P < 0.001$); on the basis of prior literature, regions of interest were selected within the blue skeleton, which included the inferior frontal gyrus and the pre-supplementary motor area (colored in orange). (c) Scatterplot showing that participants with greater FA in the right inferior frontal gyrus had better inhibitory performance (shorter SSRT) on the stop-signal task ($r_{142} = 0.24$, $P < 0.005$). From Ersche *et al* (2012a). Reprinted with permission from American Association for the Advancement of Science.

adults with stimulant dependence, their non-dependent biological siblings and 50 unrelated healthy volunteers who had neither a personal nor a family history of dependence (Ersche *et al*, 2012a, 2012b). We identified significant impairments in inhibitory control abilities and abnormally high levels of impulsive and compulsive personality traits in the sibling pairs compared with the unrelated healthy volunteers. The sibling pairs also shared abnormalities in brain regions that have previously been associated with stimulant dependence, such as the inferior frontal gyrus, the amygdale, and the putamen (Chang *et al*, 2005; Lim *et al*, 2002). Moreover, their poor performance of behavioral control on the stop-signal task was directly associated with reduced fractional anisotropy in frontal white matter brain fibers, shown in Figure 1.

These findings shed new light on addiction vulnerability and may explain why the risk of becoming addicted to drugs is increased in people with a family history. The observation that abnormalities in brain and behavior may render individuals vulnerable to developing dependence (if resilience factors are absent), opens up new avenues for preventative and therapeutic strategies. For example, preventative approaches may consider strengthening self-control abilities in individuals at risk, while therapeutic interventions could be guided by the successful compensatory strategies used by unaffected siblings to overcome their brain abnormalities in every-day life. The identification of addiction endophenotypes in brain and behavior provide further compelling evidence that drug dependence is a disorder of the brain, with underlying abnormalities that can increase a person's risk for addiction.

ACKNOWLEDGEMENTS

I would like to thank all the volunteers, without whom this study would not have been possible, and my colleagues Abigail Turton, Simon Jones, Guy Williams, Trevor Robbins and Edward Bullmore. A special word of thanks also goes to staff at the Mental Health Research Network, the Wellcome Trust Clinical Research Facility and the Wolfson Brain Imaging Center for their help and support throughout the study. This work was funded by a grant from the Medical Research Council (G0701497) and was conducted within the Behavioral and Clinical Neuroscience Institute (BCNI), which is jointly funded by the Medical Research Council and the Wellcome Trust. KDE is supported by the Medical Research Council.

Karen D Ersche[1]
[1]University of Cambridge, Department of Psychiatry and Behavioural and Clinical Neurosciences Institute, Cambridge, UK
E-mail: ke220@cam.ac.uk

DISCLOSURE
The author declares no conflict of interest.

Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T (2005). Enlarged striatum in abstinent methamphetamine abusers: A possible compensatory response. *Biol Psychiat* **57**: 967–974.
Ersche KD, Jones PS, Williams GB, Turton AJ, Robbins TW, Bullmore ET (2012a). Abnormal Brain Structure Implicated in Stimulant Drug Addiction. *Science* **335**: 601–604.
Ersche KD, Turton AJ, Chamberlain SR, Müller U, Bullmore ET, Robbins TW (2012b). Cognitive dysfunction and anxious-impulsive personality traits are endophenotypes for drug dependence. *Am J Psychiat* **169**: 926–936.
Gottesman II, Gould TD (2003). The Endophenotype Concept in Psychiatry: Etymology and Strategic Intentions. *Am J Psychiatry* **160**: 636–645.
Lim KO, Choi SJ, Pomara N, Wolkin A, Rotrosen JP (2002). Reduced frontal white matter integrity in cocaine dependence: A controlled diffusion tensor imaging study. *Biol Psychiat* **51**: 890–895.
UNODC, *Word Drug Report 2010* (United Nations Publication, Sales No. E.10.XI.13).

Neuropsychopharmacology Reviews (2013) **38,** 238–239; doi:10.1038/npp.2012.183

Epigenetic Regulation of Synapsin Genes in Mood Disorders

The synapsins are a family of neuronal phosphoproteins consisting of *SYN1* at chrXp11.3, *SYN2* at chr3p25, and *SYN3* at chr22q12.3 with alternative splicing leading to as many as 10 isoforms. They are involved in synaptic transmission and plasticity, as well as various stages of neurodevelop-

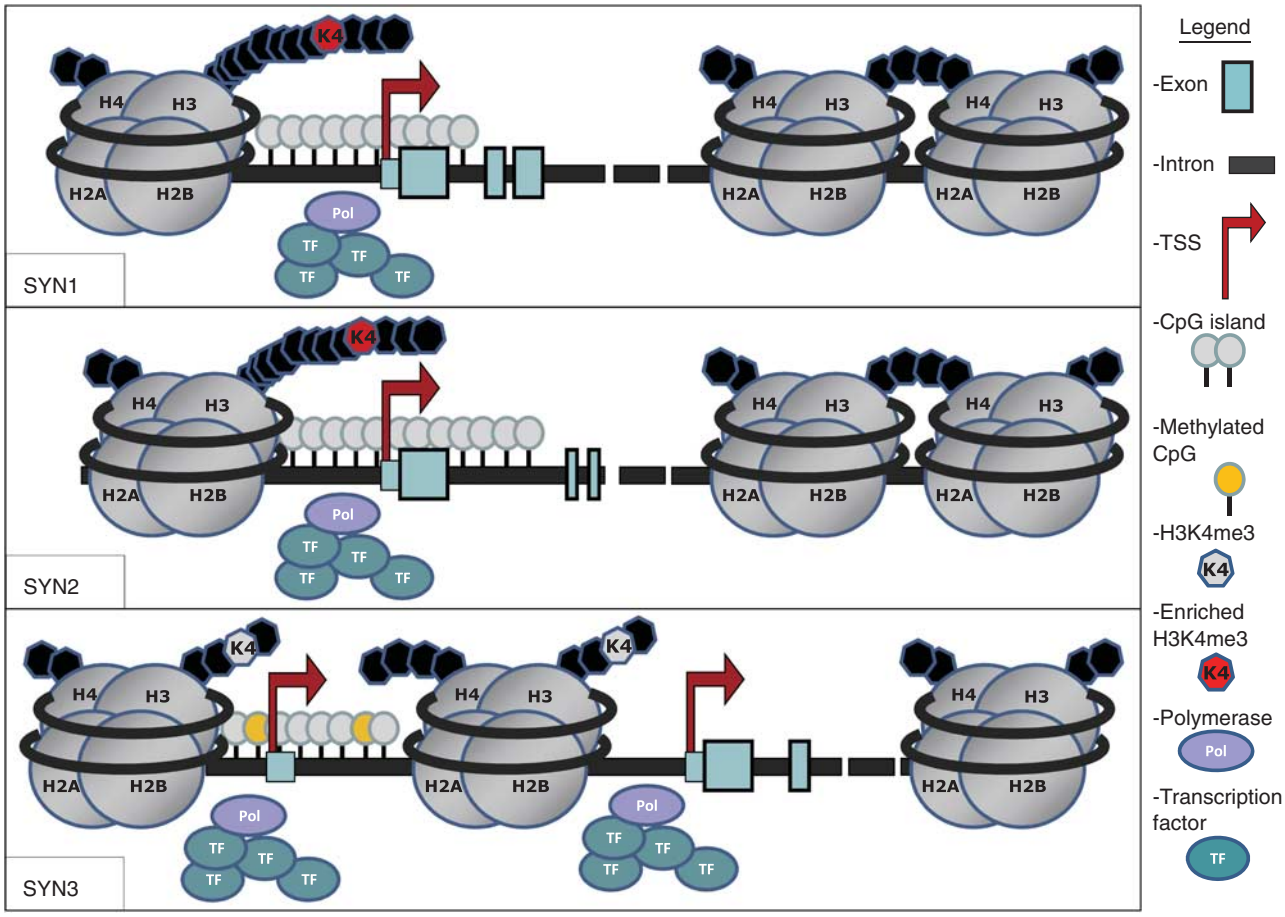

Figure 1. Potential epigenetic mechanisms at the promoter regions of synapsin genes. **Upper panel**: the *SYN1* gene (chrX:47 431 300–47 479 256). *In silico* analysis predicts a CpG island 845 bp in size at the 5′end of the gene (chrX:47 478 671–47 479 515) that spans from − 259 bp upstream of the transcription start site (TSS) to + 586 bp downstream. Evidence from chromatin immunoprecipitation assays for H3K4-trimethylation suggests that this epigenetic mark is enriched in mood disorders around roughly − 200 bp to − 350 bp upstream of the TSS. **Middle panel**: the *SYN2* gene (chr3: 12 045 862–12 233 532). The first three coding exons are represented here. *In silico* analysis predicts a CpG island of 975 bp at the 5′end of the gene (chr3: 12 045 653–12 046 627) that spans from − 208 bp upstream of the TSS to + 767 bp downstream. Evidence from chromatin immunoprecipitation assays for H3K4-trimethylation suggests that this epigenetic mark is enriched in mood disorders around roughly − 175 bp to − 400 bp upstream of the TSS. **Bottom panel**: the *SYN3* gene (chr22: 32 908 540–33 402 809). There is no predicted CpG island at the proximal promoter, but at a distal promoter upstream an alternative noncoding first exon, there is a CpG island 613 bp in size. Certain CpGs within this island have been suggested to be variably methylated in schizophrenia.

ment, including axon outgrowth and synapse formation (Cesca *et al*, 2010). All synapsins are highly concentrated at presynaptic nerve terminals of central neurons and associated with the cytoplasmic surface of synaptic vesicles, but *SYN3* has markedly distinct developmental expression and subcellular distribution, suggesting divergent function (Pieribone *et al*, 2002). Therefore, not surprisingly, a role for synapsins in neuropsychiatry has been suggested and, indeed, several studies have indicated that genetic variants at these genes can be associated with epilepsy, autism, schizophrenia, and bipolar disorder (BD) (Cesca *et al*, 2010). Furthermore, mRNA- and protein-level postmortem brain studies have suggested dysregulation of these genes in both BD and major depressive disorder (MDD) (Cesca *et al*, 2010; Cruceanu *et al*, 2012). Thus, the study of mechanisms responsible for this dysregulation in mood disorders becomes pertinent.

In the last few years, evidence has emerged suggesting that epigenetics play a role in neuropsychiatric disorders (Jiang *et al*, 2008), thus it is plausible that the dysregulation observed in synapsin expression could be attributed in part to epigenetic mechanisms. We found evidence that enrichment of H3K4me3—an epigenetic mark associated with increased transcription—at the promoters of *SYN1* and *SYN2*, but not *SYN3* is correlated with increased expression of these genes in the prefrontal cortex of patients with BD and MDD compared with controls (Cruceanu *et al*, 2012, see Figure 1). These findings are encouraging, but future research should better characterize these mechanisms by exploring the role of other chromatin epigenetic marks and brain-region specificity. In addition, the role of DNA methylation, an equally important epigenetic mechanism, should be investigated. *In silico* analyses have detected rich CpG islands at the proximal promoters of *SYN1* (845 bp) and *SYN2* (975 bp), as

well as at a distal promoter of *SYN3* (613 bp) (Miklem and Hillier, 2012, see Figure 1). To date there is no evidence in the literature of altered DNA methylation at synapsins in mood disorders, although one study of a single schizophrenia patient suggests potentially variably methylated sites in the distal CpG island of *SYN3* (Murphy *et al*, 2008). Interestingly, the CpG islands at *SYN1* and *SYN2* are immediately preceded by regions of enriched H3K4me3 in mood disorders (Cruceanu *et al*, 2012, see Figure 1). The same is not true for *SYN3*, and considering this gene's distinct expression profile and potential implication throughout neurogenesis (Pieribone *et al*, 2002), perhaps different mechanisms regulate *SYN3*. The figure illustrates our current knowledge of the synapsin genes' structure, as well as the epigenetic mechanisms that have been identified in psychiatric disorders to date.

In conclusion, brain expression differences seen in synapsin genes in mood disorders may be explained in part by differences in H3K4me3. These results need additional and independent confirmation. Moreover, considering that promoter DNA methylation can modulate gene expression and lead to neuropsychiatric phenotypes, a study of DNA methylation patterns at the synapsin promoters is warranted. On the basis of growing evidence suggesting that epigenetic mechanisms may be involved in altered regulation of synapsins in mood disorders, it would be of interest to study these genes as potential therapeutic targets or biomarkers of treatment response. Evidence is starting to emerge pointing to epigenetic marks as potential biomarkers of treatment response. For instance, for brain-derived neurotrophic factor (*BDNF*), (Lopez *et al*, 2010) showed that promoter H3K27me3 levels could serve as a biomarker of response to citalopram in MDD, and (D'Addario *et al*, 2012) found distinct DNA methylation patterns at the *BDNF* promoter in BD patients depending on mood-stabilizer and antidepressant therapy. Although no such evidence has yet emerged for synapsins, a recent study showed that lithium, one of the most commonly prescribed drugs for BD, can modulate *SYN2* expression in neuronal cell types (Cruceanu *et al*, 2012). Thus, an investigation of synapsin epigenetics in the brain compared with the periphery would be an interesting next step in elucidating their potential to serve as biomarkers for mood disorders or their treatment.

ACKNOWLEDGEMENTS

This work was supported by the Canadian Institute of Health Research (CIHR) grant MOP64410 to GT, MA, and GAR, and CIHR grant MOP119430 to GT.

Cristiana Cruceanu[1], Erika Freemantle[1], Martin Alda[2], Guy A Rouleau[3] and Gustavo Turecki[1]

[1]McGill Group for Suicide Studies, Douglas Mental Health University Institute, McGill University, Montreal, QC, Canada; [2]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada; [3]Centre of Excellence in Neuromics, CHUM Research Center and the Department of Medicine, University of Montreal, Montreal, QC, Canada
E-mail: gustavo.turecki@mcgill.ca

DISCLOSURE
The authors declare no conflict of interest.

DISCLAIMER
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Cesca F, Baldelli P, Valtorta F, Benfenati F (2010). The synapsins: key actors of synapse function and plasticity. *Prog Neurobiol* **91**: 313–348.

Cruceanu C, Alda M, Grof P, Rouleau GA, Turecki G (2012). Synapsin II is involved in the molecular pathway of lithium treatment in bipolar disorder. *PloS one* **7**: e32680.

Cruceanu C, Alda M, Nagy C, Freemantle E, Rouleau GA, Turecki G (2012). H3K4 tri-methylation in synapsin genes leads to different expression patterns in bipolar disorder and major depression. *Int J Neuropsychopharmacol* **9**: 1–11.

D'Addario C, Dell'Osso B, Palazzo MC, Benatti B, Lietti L, Cattaneo E *et al* (2012). Selective DNA methylation of BDNF promoter in bipolar disorder: differences among patients with BDI and BDII. *Neuropsychopharmacology* **37**: 1647–1655.

Jiang Y, Langley B, Lubin FD, Renthal W, Wood MA, Yasui DH *et al* (2008). Epigenetics in the nervous system. *J Neurosci* **28**: 11753–11759.

Lopez JP, Mamdani F, Labonte B, Beaulieu MM, Yang JP, Berlim MT *et al* (2012). Epigenetic regulation of BDNF expression according to antidepressant response. *Mol psychiatry;* doi:10.1038/mp.2012.38.

Miklem G, Hillier L (2012). UCSC CpG islands track (unpublished) based on Gardiner-Garden M. and Frommer M. CpG islands in vertebrate genomes. *J Mol Biol* **196**: 261–282.

Murphy BC, O'Reilly RL, Singh SM (2008). DNA methylation and mRNA expression of SYN III, a candidate gene for schizophrenia. *BMC Med Genet* **9**: 115.

Pieribone VA, Porton B, Rendon B, Feng J, Greengard P, Kao HT (2002). Expression of synapsin III in nerve terminals and neurogenic regions of the adult brain. *J Comp Neurol* **454**: 105–114.

Neuropsychopharmacology Reviews (2013) **38,** 239–241; doi:10.1038/npp.2012.186

Neuroinflammation and Autism: Toward Mechanisms and Treatments

Autism spectrum disorders (ASDs) were originally described by Kanner (1943). The relatively consistent clinical phenotype will likely be shown to comprise numerous etiologic subtypes. Approximately 10% of ASD cases are linked to disorders of genetic etiology, such as Fragile X syndrome, tuberous sclerosis, and Rett disorder. The majority of cases, however, remain idiopathic.

A role for immunological involvement in ASDs has long been hypothesized. Kanner did not comment on this in his initial descriptions, but a detailed review of the original 11 cases reveals important observations. One patient was 'kept in bed often because of colds, bronchitis, chickenpox, streptococcus infection, impetigo and rheumatic fever'. Another was 'given anterior pituitary and thyroid preparations and her father, aged 36 years, was one of those chronically thin persons, nervous energy readily expended', suggesting hyperthyroidism.

In our clinical work and review of the literature, we have been impressed by the possible role of autoimmune disorders as influencing the pathophysiology of a distinct, objectively defined etiologic subtype of ASDs. Money *et al* (1971) published what is widely accepted as the first connection between autism and autoimmune disorders. They described a family in which the youngest child had multiple